

Best of the 2001 AUA Annual Meeting

*Highlights of the 2001 Annual Meeting of the American Urological Association
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The Contributing and Medical Editors of *Reviews in Urology* were among the more than 15,000 attendees of the 2001 American Urological Association (AUA) Annual Meeting in Anaheim. Here, they report on the latest developments in their respective areas of expertise.

Can We Rebuild the Lower Urinary Tract with Stem Cell Tissue Engineering?

What makes the presentation by Chung and colleagues¹ at the AUA meeting newsworthy? The work is on the “hottest” topic of medical research: stem cells. Not a week goes by without another important new discovery in stem cell research being published in the two premiere scientific journals, *Nature* and *Science*. Let’s take a look at what this basic research may mean to the practicing urologist.

The research team successfully used stem cell tissue engineering to restore deficient urethral sphincter muscles in animal models. These findings are exciting on many levels. This is the first time that stem cell tissue engineering has been used to restore deficient sphincter muscles, and it lays the foundation for further investigation into methods of using stem cells to treat stress urinary incontinence.

In the study, researchers isolated muscle-derived stem cells (MDSC) from normal rats, transduced them with a reporter gene, and injected the stem cells into allogenic denervated proximal urethral sphincters. After 2 weeks, urethral muscle strips were prepared from normal, denervated, and denervated-MDSC injected rats. Fast-twitch muscle contractions were recorded after electrical field stimulation. The amplitude of fast-twitch

muscle contractions was decreased in denervated sphincters and was improved by approximately 88% in denervated sphincters injected with MDSC. Histological evaluation revealed the formation of new skeletal muscle fiber at the urethral sphincter injection sites.

Stem cells have the ability to divide for indefinite periods, giving rise to specialized cells. With the proper signals, the cells can develop into different types of cells. This has led researchers to investigate the theory that it should be possible to regenerate injured tissue through the injection of stem cells.

Urinary incontinence affects 13 million Americans. Those with stress urinary incontinence involuntarily lose urine while doing activities that put stress on the abdomen, such as laughing, sneezing, coughing, lifting,

or walking. A result of damage to the urethral sphincter, stress incontinence is most often caused by childbirth, menopause, or pelvic surgery.

[Michael B. Chancellor, MD]

Prostatitis: An Important Topic at the 2001 AUA Annual Meeting

The 2001 AUA Annual Meeting was a watershed for prostatitis research. It has been many decades since a whole session (in this case a poster session) was devoted entirely to this subject.

The natural history of CP/CPPS seems to be one of fluctuation, with some patients experiencing definite improvement over a 1-year time period.

Basic science and clinical research have progressed to the stage where, this year, the results of well-funded and well-designed studies by dedicated researchers have begun to tease out some of the mysteries of the epidemiology, etiology, and treatment of this enigmatic urologic condition. It is hoped that this exciting trend in prostatitis research will translate into a better understanding of the disorder and improved therapy for patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

Epidemiology. As part of a population-based, cross-sectional survey to evaluate lower urinary tract symptoms and erectile dysfunction in Singapore, Tan and colleagues included a number of questions from which a diagnosis of prostatitis could be inferred.² They concluded that 2.5% of Singapore men (mainly ethnic Chinese) aged 20 to 70 years have prostatitis-like symptoms. These patients have significantly worse erectile function and quality of life than patients without such symptoms.

As part of their ongoing longitudinal study of lower urinary tract symptoms in men in the benign prostatic hypertrophy (BPH) age group, Roberts

and colleagues evaluated prostatitis-like symptoms in a random sample of men aged 40 to 79 years selected in 1990.³ In this 1998 survey, the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) pain and urinary domains were completed to evaluate prostatitis-like symptoms. Sixteen percent of the men in this survey reported a pain score greater than or equal to 1, with over 20% of men reporting significant prostatitis-like symptoms. Because

this was essentially a cohort of men selected in 1990 for a survey that was designed to evaluate BPH or lower urinary tract symptoms (LUTS), by the time the survey was completed, all the men in the cohort were more than 49 years old, and it was missing the very important and common patient presenting with prostatitis at a much younger age.

Two presentations, one from a population-based cohort from Canada by Nickel and colleagues and the other on a cohort of patients clinically diagnosed with CP/CPPS by O'Leary and colleagues, confirmed that over a 1-year follow-up period, one third to one half of men with prostatitis-like symptoms (population-based study) or with a clinical diagnosis of chronic prostatitis (CP/CPPS cohort study) improve slightly, while most men have stable symptoms or worsen.^{4,5} The natural history of CP/CPPS seems to be one of fluctuation, with some patients experiencing definite improvement over a 1-year time period.

Calhoun and colleagues examined the impact of a chronic prostatitis diagnosis on health care costs.⁶ They undertook a health care utilization inventory in 79 men enrolled in the

NIH Chronic Prostatitis Cohort Study and concluded that chronic prostatitis is associated with substantial financial costs (not to mention many socioeconomic costs). Extrapolated to the entire U.S. population, this diagnosis represents hundreds of millions and perhaps even billions of dollars in direct and indirect costs.

Etiology. A number of studies shed some light on possible etiologic mechanisms in prostatitis. Jarvi and colleagues employed molecular biological methods to detect microbial organisms that are difficult or impossible to culture and reported two previously undetected species in prostatitis patients.⁷ *Paenibacillus spp.* and *Proteobacterium spp.* were the most common bacteria they found in men with category III CP/CPPS; the same bacteria were significantly less common in asymptomatic controls. This association raises intriguing questions on whether these microorganisms are causative or just opportunistic organisms in patients with CP/CPPS.

A number of specific markers were identified in prostatitis patients that may assist in the diagnosis and follow-up of patients and may suggest further avenues for finding therapeutic targets. Shoskes and colleagues confirm that men with CP/CPPS have high levels of inflammatory markers (PGE-2) and low levels of the natural opioid beta-endorphins.⁸ Freyle and colleagues measured serum cytokines in patients with elevated prostate-specific antigen (PSA) levels and abnormal digital rectal examination results.⁹ They discovered that levels of the pro-inflammatory cytokines interleukin-2 and tumor necrosis factor-alpha were significantly elevated in patients with biopsy-proven prostatic inflammation (prostatitis) compared to levels in patients with prostate cancer. In patients with elevated PSA, the detection of elevated pro-inflammatory cytokines may be

helpful in differentiating asymptomatic inflammatory prostatitis from cancer of the prostate. Dimitrakov and colleagues identified procalcitonin as a reliable marker of prostate tissue damage.¹⁰ Elevated procalcitonin levels predicted a favorable response to antibacterial therapy in this group of CP/CPPS patients.

It has been traditional practice to identify uropathogenic bacteria and white blood cells in prostate-specific

one of eight patients who responded to placebo at 3 months. At 1 year, sustained improvement was seen in four of seven patients with active treatment and in one of five patients on placebo. Further follow-up and larger studies will determine the durability and repeatability of these particular responses.

Volpe and colleagues randomized 64 men with CP/CPPS to 1 year of therapy with either saw palmetto or

were responders (defined as having either a 25% decrease in total symptom score or a 6-point improvement in total symptom score), and there were significant improvements in subjective assessments in the 50-mg rofecoxib group compared with those in the placebo group. Rofecoxib was well tolerated at both doses. Further studies are needed to assess anti-inflammatory therapy in the treatment of prostatitis.

[J. Curtis Nickel, MD, FRCSC]

A comprehensive evaluation of the first 278 men screened in the NIH Chronic Prostatitis Cohort Study...showed that degree of inflammation and infection did not correlate with severity of symptoms.

specimens in patients presenting with CP/CPPS. A comprehensive evaluation of the first 278 men screened in the NIH Chronic Prostatitis Cohort Study presented by Schaeffer and colleagues showed that degree of inflammation and infection did not correlate with severity of symptoms.¹¹ These findings suggest that factors other than inflammation and infection contribute to symptoms associated with CP/CPPS. Andersen and colleagues confirmed that in their series of 38 men referred to the Stanford Prostatitis Clinic, prostate inflammation did not correlate with greater pain.¹² (Actually, they found that men without inflammation generally had higher pain scores.) Furthermore, there was no significant difference in clinical response to physiotherapy or prostate massage in those with or without inflammation.

Treatment. Three prospective randomized controlled studies evaluating treatment modalities for CP/CPPS were reported this year. Patel and colleagues randomized 20 men, who received either active electromagnetic therapy or placebo.¹³ Five of eight patients receiving active treatment had successful outcomes, compared to

finasteride.¹⁴ At the end of the trial, 13 of 32 (27%) and 19 of 32 (59%) opted to continue saw palmetto and finasteride, respectively. Patients on finasteride had a significant improvement in total prostatitis score, pain subscore, and quality of life assessment compared to those taking saw palmetto that was evident by 6 months of therapy.

Nickel and colleagues reported the results of the largest randomized placebo-controlled trial ever undertaken in CP/CPPS.¹⁵ This was a pilot study to determine the effects of

Tumor Markers and Diagnosis

Once again prostate cancer was the dominant theme at the 2001 AUA meeting. Fully 375 (23%) of the papers presented dealt with prostate cancer, and 94 of these dealt with tumor markers. As such, once again it is exceedingly difficult to pick the best—and besides, my mother always taught me there is no best! Papers that I think are deserving of special mention are reviewed here.

Vis and colleagues¹⁶ and Mäkinen and colleagues¹⁷ from the Netherlands and Finland, respectively, clearly demonstrate the ineffectiveness of the digital rectal examination in screening men with low PSA. Given the significance of cancer found at these low PSA levels, these papers suggest that

Cancer found on the third and fourth biopsies had significantly lower pathologic risk potential.

treatment with rofecoxib, a COX-2-selective inhibitor, versus placebo in patients with chronic prostatitis. Following a 1-week placebo run-in, 161 patients were randomized to 6 weeks of treatment with rofecoxib 25 mg or 50 mg or with placebo. All three groups had significant improvements in NIH-CPSI, but the differences between groups were not significant. Significantly more patients

lowering the cutoff level, as has been done in these prospective studies, to 3.0 ng/mL or greater may be the most appropriate testing regimen. Several papers addressed the need for repeat biopsy. The St. Louis group¹⁸ and a multicenter European study¹⁹ demonstrate the significance of prostate cancer found on the initial repeat biopsy. However, the multicenter European trial showed that cancer

found on the third and fourth biopsies had significantly lower pathologic risk potential.

Many papers addressed the issues of prostatic intraepithelial neoplasia (PIN) and atypia on the initial biopsy. These were represented in abstracts 401 to 404.²⁰⁻²³ Virtually all studies have demonstrated significant risk of finding cancer on repeat biopsy when these pathologic features are identified. A study from the Netherlands²⁰ failed to confirm this finding. Moreover, Lefkowitz and colleagues²³ also showed that in men who had an

The authors demonstrated that complex PSA (cPSA) provides greater diagnostic performance over total PSA (tPSA). Further enhancement in identifying men with prostate cancer was demonstrated with the ratio of cPSA to tPSA. Abstract 1165²⁶ also evaluated cPSA in comparison to tPSA and demonstrated a similar advantage in the detection of prostate cancer. In a further refinement of these studies, abstract 1271²⁷ evaluated tPSA compared to the free/total ratio and the cPSA in men with a tPSA between 2.5 and 4.0 ng/mL. These

continues to surround the issue of insulin-like growth factor (IGF) and its binding proteins. Abstract 842³³ refuted previous results indicating predictability of progression for prostate cancer risk with these markers. However, in a similar study³⁴ the authors demonstrated that IGF binding protein 2 was elevated in men with prostate cancer and IGF binding protein 3 decreased in men with metastatic disease.

[Michael K. Brawer, MD]

Considerable effort remains under way to make PSA more specific.

initial 12-core biopsy experience, isolated high-grade PIN did not result in a significant finding of cancer on repeat biopsy. What would seem to be emerging from these studies is that as we increase the number of initial biopsies, the finding of PIN in the absence of carcinoma is an increasingly rare event. The impressive yield in repeat biopsy in high-grade PIN previously observed might be related in large part to undersampling in historical series. For example, in our original study we only biopsied "suspicious areas"; this investigation antedated the sector approach.²⁴ These considerations must be reflected upon as the clinician evaluates the risk of missed carcinoma in his or her patients.

Considerable effort remains under way to make PSA more specific. In this regard, the simplest test has been the complex form of PSA. Partin and associates²⁵ presented the preliminary results of a seven-site prospective evaluation of complex PSA in the early detection of prostate cancer. In this study 539 men, 35% of whom had prostate cancer, were evaluated with total PSA and complex PSA. It was primarily prospective in nature.

The authors demonstrated that the cPSA and the computed cPSA (defined as total PSA minus free PSA) were more specific than the free-to-total PSA ratio in detecting prostate cancer.

A number of authors have historically looked at the ratio of free to total PSA as an independent predictor of aggressiveness of prostate cancer. Four studies²⁸⁻³¹ evaluated this phenomenon. The first two failed to demonstrate a significant predictability of pathologic stage or biochemical recurrence based on the free-to-total PSA ratio. The latter two studies did suggest some benefit in predicting pathologic stage.

The search for novel serum markers for better diagnosis and prognostic information in men with prostate cancer goes on. Transforming growth factor (TGF) β was shown to strongly predict progression in men with prostate cancer, as shown in abstract 841.³² These authors demonstrated significantly that TGF β levels are markedly elevated in men with metastatic disease. In men without documented metastasis the TGF β level is a strong predictor of progression, indicating probable detection of an occult metastasis. Controversy

Radiographic Methods to Diagnose Obstruction

The pediatric podium and poster sessions at the AUA meeting included many presentations of innovative clinical and basic research. The highlights of the clinical presentations were two abstracts on radiographic methods to diagnose obstruction.

Dr. Houle and colleagues³⁵ from Montreal presented a new approach to the diuretic renogram. They proposed the use of a new classification that does not utilize the $T_{1/2}$ time; rather, it utilizes a quantified image at 90 minutes following Lasix injection. From this image, they calculate a delayed washout ratio (90'/20'). They evaluated only those patients with dilation associated with the renal pelvis. None of the patients had reflux. From these data, they developed the following classification: Class 0: pre-diuretic washout was $\geq 70\%$; Class 1: 20' post-diuretic washout (PDW) $> 40\%$ and 90'/20' PDW $> 50\%$; Class 2: 20' PDW \leq to 40% and 90'/20' PDW $> 50\%$; Class 3: 20' PDW \leq to 40% and 90'/20' PDW \leq 50%. Their study shows that 50% of Class 3 patients require surgery versus only 7.5% of those in Classes 0, 1, and 2. The patients with the highest severity of obstruction underwent surgery within 2.2 months, whereas the occasional Class 1 and 2 patients who ultimately underwent surgery

were followed for as long as 34 and 41 months, respectively, before showing deterioration. They conclude that this new classification provides improved stratification of patients with dilation of the upper urinary tract.

Dr. Perez-Brayfield and associates³⁶ in Atlanta investigated dynamic contrast-enhanced magnetic resonance imaging (MRI) of renal function in children with hydronephrosis. They

uation of hydronephrosis in children. [Ellen Shapiro, MD]

Minimally Invasive Surgery

Upper urinary tract transitional cell carcinoma. Sung and colleagues³⁷ presented their extensive experience with laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma. Their procedure is based on two stages. The cystoscopic

This new classification provides improved stratification of patients with dilation of the upper urinary tract.

compared this test with renal ultrasound and ^{99m}Tc-DTPA scintigraphy, which have been used as the standard radiographic tests for the evaluation of children with obstructed uropathy. The dynamic contrast-enhanced MR imaging was performed in 17 children ranging in age from 3 weeks to 9 years. None of the patients had reflux. Standard T1 and T2 spin echo images were obtained. Dynamic perfusion imaging was obtained after intravenous administration of gadolinium. Images were obtained every 15 seconds for 3 minutes, and every 30 seconds for 12 minutes. Lasix was administered after 15 minutes, and imaging proceeded for an additional 15 minutes. Relative renal function and time activity curves were calculated. This study shows that MRI provides superior morphologic imaging over ultrasound and renal scintigraphy. No difference was found in the relative renal function calculated by MRI and by renal scintigraphy. Further studies need to be performed to determine reliably the drainage curves, because they currently vary due to changes in signal intensity related to the concentration of the contrast medium. This study is an important step forward toward developing an imaging modality that is reliable in the eval-

management of intramural ureter is combined with the radical nephrectomy that is performed in a retroperitoneal fashion. Twenty-seven of the 60 patients were discharged within 24 hours, with average hospital stays of just over 2 days. A complication rate of 11.6% was noted, and 18% of the patients had bladder recurrence, all of which were treated cystoscopically. There was no local or port site recurrence.

As compared to open radical nephroureterectomy, the lower convalescence, complication rate, and surgical time were statistically significant. The authors conclude that laparoscopic retroperitoneal radical nephroureterectomy has become the

techniques was presented by Rotariu and colleagues.³⁸ This is a benchmark presentation in that it represents the largest series in the literature of patients with a single renal unit and high-grade transitional cell carcinoma who were treated endoscopically. The authors used a combination of percutaneous and retrograde ureteroscopic techniques as well as adjuvant topical bacillus Calmette-Guerin. They compared their data to a matched group of patients who underwent radical nephroureterectomy and hemodialysis. The overall survival rate was longer in patients treated endoscopically as compared to those undergoing radical surgery. The surgical complication rate was similar in both groups, but those undergoing radical surgery had a higher rate of cardiovascular events during the following year after the procedure. The authors propose that endoscopic treatment is preferable in this select patient population because survival is short in this group no matter which treatment is chosen. They suggest that the improved quality of life off dialysis is a significant factor in choosing this treatment as compared to rendering a patient anephric.

Parenchymal renal malignancies. The Cleveland Clinic experience in complex open partial nephrectomy was compared to a growing group of patients undergoing laparoscopic

This is a benchmark presentation in that it represents the largest series in the literature of patients with a single renal unit and high-grade transitional cell carcinoma who were treated endoscopically.

standard in treating those select patients with upper urinary tract transitional cell carcinoma who require extirpative surgery.

An extensive 15-year experience with high-grade upper urinary tract transitional cell carcinoma in a solitary kidney treated with percutaneous

partial nephrectomy. Dr. Gill's group³⁹ is striving to maintain the same surgical principles that Dr. Novick's group³⁷ espouses and applies to some of the most complex renal malignancies. This study is based on one and one half year's experience with 36 patients who underwent laparoscopic

partial nephrectomies, half of which were performed in a purely retroperitoneal fashion. The steps in preparing the kidney and performing the partial nephrectomy were identical to those employed at the same institution for open partial nephrectomy.

There were no open conversions in this series, and the mean operative time was approximately 3 hours. The warm ischemia time was on average 20 minutes, and the blood loss was minimal at 237 mL. The authors updated their data at presentation with three cases of intraoperative

There were three partial responders, patients with large, centrally located tumors. Complications included ureteral obstruction requiring stent placement in two patients and gross hematuria with perinephric bleeding managed conservatively in one patient.

Pavlovich and colleagues⁴¹ employed a 15-gauge radiofrequency needle with deployable tines placed into the tumor, creating a larger defect. This was performed percutaneously under conscious sedation using either ultrasound or CT guidance. Follow-up was based on CT scan and nuclear medicine

They suggested that the smaller instruments and other improvements, including new accessories and endoscopic lithotrites, combine to improve their overall success while decreasing complications. They presented their data in three groups. The first group was patients accrued between 1982 and 1985, the second was patients accrued up to 1992, and the third was current study data. The major complication rate, that is, the risk of ureteral stricture from therapeutic ureteroscopy, decreased to no patients in the third, most recent group. Their success rate for ureteroscopic treatment of all stones throughout the upper urinary tract was over 90%, with the highest rate being in the distal ureter.

Dr. Bagley⁴³ presented a prospective study in which various-sized flexible ureteroscopes were tested with regard to ease of placement. He found a statistically significant difference between 9 French and smaller, <8 French endoscopes. These endoscopies were all performed without an operating sheath. In those patients who initially underwent a trial of 9 French flexible ureteroscopy, 33% of procedures failed due to inability to place the endoscope without ureteral dilation. It should be noted, though, that failure to pass an 8.4 French ureteroscope was noted in only two patients out of 38, and only one patient could not have the smaller 7.4 French endoscope passed successfully. It was Dr. Bagley's belief that the decrease in size of the endoscope from 9 to 8.4 French did not affect the rate of breakage and repair of the instruments. He did feel, however, that with the current state of technology, decreasing below this size at this time does produce a more fragile instrument.

Ureteropelvic junction obstruction. Desai and colleagues⁴⁴ present a novel endourologic technique to repair a ureteropelvic junction (UPJ)

Both these studies present a fascinating new treatment for renal malignancy.

renal hypothermia using saline slush instilled and then removed from the renal bed. Complications included inadvertent enterotomy as well as two patients with cardiopulmonary events. The majority of the lesions were primary renal cell carcinoma. The authors believe that there is a transition from open to laparoscopic techniques and that initially patients with exophytic and smaller lesions will be selected but in the future, as technology improves, the majority of partial nephrectomies will be performed employing laparoscopic techniques.

In comparison to the prior study of laparoscopic partial nephrectomy, two groups presented their experiences with percutaneous radiofrequency ablation of small renal malignancies in patients with secondary comorbidities who were not candidates for radical surgery. McGovern and colleagues⁴⁰ treated tumors as large as 5.5 cm, with the radiofrequency electrode being placed either under ultrasound or computed tomography (CT) guidance. Follow-up was then performed with CT or MRI. Patients were followed from 6 months to 3 years. All patients were treated with an intent to cure.

renography as well as appropriate urine and serum studies. Of the 22 patients, 19 were available for follow-up at 6 months. All but one patient were discharged within 24 hours after the procedure. There were no major complications in this series and no significant change in renal function. The tumor diameter decreased on average from 2.4 to 1.7 cm at 6 months posttreatment.

Both these studies present a fascinating new treatment for renal malignancy. This may be particularly useful in patients who, because of comorbidities, are not surgical candidates for traditional partial or radical nephrectomy. The follow-up in both groups is short, but the preliminary indication is that these lesions may shrink and disappear after thermal therapy. Careful follow-up of these two cohorts of patients will be particularly important to validate this treatment.

Upper urinary tract endoscopy. The first study is an update of an extensive database from the Mayo Clinic that spans just less than 20 years. Dr. Segura's group⁴² carefully defined the decreasing complication rate with therapeutic ureteroscopy.

obstruction. This is a combination of endopyelotomy and laparoscopic pyeloplasty performed on an animal model. The authors used a pig model in which the ureters were tied and a stricture developed and then performed antegrade endopyelotomy through a standard access sheath. After the endoscopic incision was performed in a longitudinal, posterior lateral fashion, a laparoscopic suturing device was placed through the nephroscope, and the pyelotomy was closed with interrupted sutures transversely.

This repair produced a widely patent UPJ, which was significantly larger than the endopyelotomy-only control group. In addition there was significantly less extravasation noted. This reflects a preliminary animal study, but the potential is significant. The combination of these two techniques may facilitate a prompt watertight repair without the need for an ureteral stent. It will be interesting to see how this early data compares with the initial clinical trials of this technique.

[Michael Grasso, III, MD]

Prostate Cancer: Early Detection and Screening

Since the early 1990s, there has been an unprecedented decrease in prostate cancer mortality rates, which has been documented in the United States and several countries worldwide. Although many have attributed this decrease in mortality to widespread and affective use of PSA testing and early detection algorithms, a direct correlation between early detection programs and cancer-specific mortality rates has yet to be proven. At this year's AUA meeting, Boyle and associates, from Milan, Italy, documented trends in prostate cancer mortality worldwide.⁴⁵ They demonstrated that the decline in mortality rates is not a feature that has been recognized in every country. However, many countries, particularly

those in which PSA screening has been widespread for the last decade, have in fact noticed declines in prostate cancer mortality rates.

Boyle and associates investigated prostate cancer mortality trends in several European countries, Canada, Australia, New Zealand, and Japan, as well as in the United States. They calculated an age-standardized mortality rate employing the World Standard Population as the standard. These data demonstrated that the median age of prostate cancer death

change in cause-of-death coding in the United Kingdom, which took place in 1985, could be associated with this rapid decrease in prostate mortality rates seen in elderly men. The authors believe that this was not the case in the other countries. The authors believe that the patterns and level of prostate cancer mortality in the United States and Canada do in fact support the hypothesis that widespread PSA testing is efficacious. Likewise, the increasing mortality rate trend in Sweden would

These data represent some of the strongest arguments supporting the hypothesis that prostate cancer screening has affected overall prostate mortality rates worldwide.

was 79 years, which is higher than that seen for either breast or colorectal cancer. The age of diagnoses in two countries in which prostate cancer screening is widespread (United States and Canada) was younger than in other countries; however, the median age at death for these countries was similar to that in other countries. A major decline in the mortality rate for prostate cancer in men over age 50 was documented for the United States, the United Kingdom, Canada, France, and Austria. Several other countries, including Australia, Belgium, Finland, Greece, Germany, Japan, Norway, Spain, and others were either stabilizing mortality rates or had rates that continued to increase.

It has been interesting to note that the United Kingdom, a country not known for prostate cancer screening, was among those countries demonstrating major declines in prostate cancer mortality. The authors explain this as a function of changes in death certificate coding, because the decline in prostate cancer death in the United Kingdom was only evidenced in patients over age 80. The

indicate that a lack of prostate cancer screening has not been successful in reducing mortality rates. Mortality decreases in Austria were compatible with an impact of widespread PSA testing, as previously noted by the group from Tyrol county. The authors conclude by warning that, although these data do not prove the hypothesis that widespread PSA testing in these populations has caused these decreases in prostate cancer mortality, clearly they support this hypothesis. The authors also caution against interpretation of prostate cancer trends based on their work.

These data represent some of the strongest arguments supporting the hypothesis that prostate cancer screening has affected overall prostate mortality rates worldwide.

[Alan W. Partin, MD, PhD]

Benign Prostatic Hyperplasia

This year 80 abstracts concerning benign prostatic hyperplasia (BPH) were accepted for presentation in either a poster or podium session during the annual meeting of the AUA in Anaheim. This represents approxi-

Table 1
Results from a Trial of BPH and LUTS Patients Randomized to Receive Either Tamsulosin or Saw Palmetto Extract: Changes in Evaluation Criteria at 12 Months

	I-PSS	QOL	Q _{max}	MSF-4	PV	Total PSA
Baseline tamsulosin	15.4 (5.2)	3.2 (1.1)	11.2 (4.0)	7.7 (5.0)	48.0 (19.0)	2.7 (2.2)
Changes	-4.4 (5.1)	-1.0 (1.2)	1.8 (4.8)	0.4 (3.5)	0.2 (12.8)	0.2 (1.6)
Baseline LSESr	15.3 (4.3)	3.1 (1.0)	10.9 (3.9)	8.3 (5.3)	48.0 (18.0)	2.5 (1.9)
Changes	-4.4 (5.5)	-0.9 (1.1)	1.9 (54.8)	0.5 (3.3)	-0.9 (13.4)	0.3 (1.4)

I-PSS, International Prostate Symptom Score; QOL, disease-specific quality of life score; Q_{max}, peak urinary flow rate; MSF-4, male sexual function questionnaire; PV, prostate volume; PSA, prostate-specific antigen; LSESr, lipido-sterol extract of *Serenoa repens*.

Results are given as mean values (SD).

mately 5% of all 1611 abstracts accepted, a number that has been consistent over the past 5 years. In these 80 abstracts, the interest was equally divided among medical and hormonal therapy, surgical therapy, and new technologies, also now known as minimally invasive surgical therapies (or MIST) interventions.

The study of phytotherapeutic agents in the treatment of LUTS and BPH is generating more and more interest from year to year. This interest is partially driven by patients looking for "natural" therapeutic alternatives, the direct consumer advertisement conducted by an ever-growing number of companies producing phytotherapeutic agents for a variety of prostate conditions, and by the attempt of the urologic scientific community to study these agents in terms of their composition, mechanism of action, and clinical efficacy and safety. The most popular of these agents is the extract from the berries of the American dwarf palm tree (*Serenoa repens*), known as saw palmetto extract. In the United States alone, there are over 30 products available in health food stores and for over-

the-counter sale that contain saw palmetto together with other ingredients. Several abstracts were presented examining the role of these compounds in the treatment of men with LUTS and clinical BPH.

Coulange and colleagues⁴⁶ report on a multi-center, randomized, double-blind, 1-year study comparing the efficacy, tolerability, and safety of the α adrenergic receptor blocker tamsulosin with a combination of tamsulosin and saw palmetto extract. A total of 352 patients were enrolled in 74 centers in France. After a 2-week placebo run-in, 329 patients were randomized to receive these treatments over a period of 52 weeks. The authors report a decrease in International Prostate Symptom Score (I-PSS) score of -5.2 ± 6.4 points in the tamsulosin and -6.0 ± 6.0 points in the tamsulosin plus saw palmetto groups ($P = .286$, not significant). Other instruments were also used to assess efficacy; however, the differences were not significant for either the UroLife 9-question item, or the single disease-specific Quality of Life question attached to the I-PSS score. Changes were -1.0 and -1.3 points

for the two groups, respectively. Sixty-four percent of the tamsulosin-treated and 69% of the combination treatment group were classified as responders, based on the symptom score (not significant). Discontinuation due to adverse events occurred in nine patients in the tamsulosin and 15 patients in the tamsulosin plus saw palmetto extract group. The authors conclude, therefore, that the addition of saw palmetto does not add to the overall efficacy of the α blocker. Unfortunately, this large trial conducted over 1 year suffers from a less than ideal design, by lacking a saw palmetto single agent arm or a placebo control group.

A group from Europe⁴⁷ conducted a double-blind, randomized, parallel group trial in 11 European countries, enrolling 811 men with LUTS and clinical BPH for a 52-week trial with a 4-week placebo run-in period. Patients were randomized to receive either tamsulosin or the specific oral Permixon, a well-studied saw palmetto extract.

Regarding all studied outcome parameters, I-PSS score, disease-specific quality of life score, peak urinary flow rate, male sexual function ques-

tionnaire, and prostate volume, there were no differences between the two groups. The only difference occurred regarding ejaculatory disorders, which were seen in 15 (4.2%) of tamsulosin-treated patients versus 2 (0.4%) of the Permixon-treated patients ($P = .045$) (see Table 1).

The scientifically most exciting data were presented by a group of investigators who over the past few years have steadily improved our understanding of the mechanism of action and the effect of saw palmetto extract on the morphometry of the benignly enlarged prostate. This group of investigators, led by Dr. Leonard Marks, presented three abstracts describing the methods for quantification of androgenic steroid hormones in the prostate on needle biopsies,⁴⁸ the effect of saw palmetto herbal blend (SPHB) on androgenic steroids in the prostate,⁴⁹ and the effect of SPHB on the epithelial nuclei in the prostate of men with LUTS and symptomatic BPH.⁵⁰

In a landmark study, McConnell and colleagues⁵¹ treated 69 men suffering from BPH with either placebo or 1, 5, 10, 50, or 100 mg per day finasteride 7 days prior to transurethral resection of the prostate (TURP). During TURP, prostatic tissue was harvested and examined for dihydrotestosterone (DHT). The concentration of DHT in the prostate was 10.3 ± 0.6 nmol/kg,

and the mean concentration of testosterone was 0.7 ± 0.1 nmol/kg. After 7 days of treatment with all doses of finasteride, DHT levels decreased to 15% or less of controls, and the testosterone concentration increased in a reciprocal fashion. This study represents the proof-of-concept and forms the scientific

androgens represents a welcome addition to our armamentarium for the study of the tissue effects of such compounds.

In the first abstract of Marks and colleagues,³ the investigators obtained prostatic samples by transrectal ultrasound-guided biopsy from 20 men with LUTS and BPH. The prostatic

Using needle biopsy specimens to quantify intraprostatic androgens represents a welcome addition to our armamentarium for the study of the tissue effects of such compounds.

foundation for the use of 5α -reductase inhibitors, which prevent the conversion of testosterone to DHT.

In the past, several claims have been made regarding a possible 5α -reductase-inhibiting effect of saw palmetto extract. One of the limiting steps in assessing the effect of drugs on the intraprostatic androgenic steroid concentration has been the requirement for large tissue retrieval. This was either accomplished during the time of a TURP by removing a prostatic chip with as little as possible cauterization artifact, or by removing tissue by open enucleation of the prostate. In this context, the methodology presented by Dr. Hess, a veterinarian from Oregon Health Sciences University, using needle biopsy specimens to quantify intraprostatic

samples had a mean weight of 7.6 mg with a range of 1.5 to 16.2. The biopsy was done in the standard manner, using an 18-Ga needle. Of the patients, 7 were on long-term therapy with finasteride and 13 were untreated controls. The specimens were flash-frozen on dry ice and stored at -80°C . The tissues were then homogenized, and a micro-column chromatography was used to isolate individual testosterone and dihydrotestosterone fractions after extraction with diethylether. The concentration of testosterone and DHT was measured by radioimmunoassay (RIA) and expressed as ng/g of prostate tissue. The steroid recovery as determined by addition of tritiated testosterone and C-14-DHT to samples processed and parallel with RIA samples was 73% and 84% for

Table 2
Serum and Prostate Dihydrotestosterone (DHT) and Testosterone (T) Levels in 20 Men
(7 Treated with Finasteride and 13 Controls) with LUTS and BPH

	Serum DHT (ng/mL)	Serum T (ng/mL)	Tissue DHT (ng/g)	Tissue T (ng/g)
Controls	0.48 ± 0.24	4.59 ± 2.7	4.89 ± 2.1	1.89 ± 1.1
Finasteride	$0.14 \pm 0.09^*$	3.26 ± 1.6	$1.42 \pm 0.9^*$	$4.91 \pm 3.3^*$

Levels are shown as mean plus or minus SD.

LUTS, lower urinary tract symptoms; BPH, benign prostatic hyperplasia

testosterone and DHT, respectively. To determine sampling variability, a total of 10 samples from each specimen were analyzed. The sampling variability was appreciable, with a coefficient of variation of 0.23 to 0.61. However, a complete separation of finasteride-controlled patients was still possible. As Table 2 demonstrates, the ratio of DHT to testosterone in prostate tissue was 4.89/1.89 in controls, and after finasteride treatment, exhibited the typical change to a ratio of 1.42/4.91 for DHT and testosterone, respectively.

Having demonstrated the feasibility of the methods, Marks and colleagues proceeded to study the effect of SPHB on intraprostatic androgens.⁴⁹ Men with LUTS and clinical BPH underwent sextant biopsy of the prostate at baseline, and after 6 months of treatment with either placebo ($n = 20$) or a standardized SPHB containing 320 mg per day of saw palmetto extract ($n = 20$). At baseline, the prostatic levels of testosterone and DHT were similar in the two groups. Following treatment, the intraprostatic testosterone level did not change in either group, but in the SPHB group median DHT decreased to 4.4 ng/g ($P = .005$ by signed rank test), representing a 32% change from baseline. In the control group, no change was seen in the median DHT levels. Serum levels of testosterone, DHT, and estradiol were also measured, but no changes were observed. Also, no correlation was seen between tissue DHT changes and clinical changes, which were monitored in parallel (symptom score, flow rate, prostate volume, etc). Although the 32% decrease in prostatic DHT is modest compared to the changes seen after finasteride therapy, and even though there was no parallel increase in tissue testosterone or a decrease in serum PSA or serum DHT, the data presented offer (at least in the opinion of the authors) support to

the hypothesis that saw palmetto functions as a mild inhibitor of the 5α -reductase *in vivo*.

In addition to the study of intraprostatic androgenic steroid hormones, Marks and colleagues also presented data concerning the effect of SPHB on prostatic epithelial nuclei in men in the same group of patients.⁵⁰ The pathologic reference laboratory used was the laboratory of Dr. Jonathan Epstein at the Johns Hopkins Institution in Baltimore. For this particular part of the analysis, tissue from the previously mentioned sextant biopsy before and after treatment on men treated with placebo versus SPHB was subjected to a fulgen stain and quantitative imaging analysis using the Tipass Quic-DNA system. Nucleated images were captured at random, and 60 different nuclear morphometric descriptors (NMDs) (size, shape, DNA content, textural features, etc) were determined for each. At baseline, the placebo and SPHB groups were similar in their NMDs. The biopsies after 6 months of treatment showed no change in the placebo group. However, 25 of the 60 NMDs in the SPHB-treated patients differed significantly from baseline. Four of these 25 NMD alterations, a DNA content measure and three texture features, were retained in a multivariate logistical regression model, resulting in an area under the ROC curve of 93.5% ($P < .001$). These changes in nuclear morphometry were not correlated with the epithelial contraction reported before by the authors⁵² or DHT suppression as described in Abstract 1548.⁴⁹ The authors speculate that these chromosomal alterations may suggest a molecular basis for yet another mechanism of action of SPHB.

There is no question that this sequence of three abstracts represents one of the best translational research efforts to further our understanding

of the mechanism of action of saw palmetto extract in men with LUTS and clinical BPH on hormonal, cellular, and molecular levels. Further, the methodology developed by this group of investigators to measure intraprostatic steroid hormones on a biopsy specimen should facilitate such investigation by eliminating the need for the removal of large pieces of tissue by TURP or open prostatectomy. Clearly, questions remain regarding the effect of saw palmetto extracts: the reduction of DHT is significantly less than that achieved with finasteride; there is no accompanying increase in intraprostatic testosterone levels; there is no serum effect on either DHT or testosterone with the saw palmetto extract, in contrast to finasteride; there is no change even in long-term studies of serum PSA or prostate volume, a feature commonly found after finasteride treatment; and the implication of the nuclear morphometry changes in terms of clinical outcomes is as of yet undetermined.

Phytotherapeutic agents remain an important area of research for urologists, and the development of sophisticated tools as described by this group of investigators should allow more scientific progress over the upcoming years.

[Claus G. Roehrborn, MD]

Does Preoperative Chemotherapy Improve Survival in Patients Undergoing Cystectomy?

In the United States, radical cystectomy with bilateral pelvic lymph node dissection remains the gold standard for localized muscle-invasive disease.⁵³ However, 50% of patients with muscle invasion develop recurrent, metastatic disease. In an effort to decrease risk of progression, several trials have recently examined whether neoadjuvant therapy prior to cystectomy could help to shrink tumor burden, eliminate micrometastatic disease to lymph

Table 3
Results of a Trial Comparing Cystectomy
with MVAC to Cystectomy Alone in Treatment
of Locally Advanced Bladder Cancer⁵⁵

	MVAC	No MVAC	Total
Eligible patients	153	154	307
Males	127	124	251 (82%)
Age < 65	85	87	172 (56%)
Cystectomy	126	125	251 (82%)
Deaths (median follow-up 7.1 yrs)	85	94	
Median survival	6.2	3.8	

MVAC, methotrexate, vinblastine, Adriamycin, and cisplatin.

Hazard ratio: 0.74 (95% CI: 0.55-0.99, $P = .027$)

nodes and to other sites, and therefore improve patient survival.

In particular, the results of the Southwest Oncology Group (SWOG 8710)/INT-0080 were presented by Dr. David Crawford at this year's AUA meeting.⁵⁴ The randomized phase III trial of neoadjuvant methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC) and cystectomy versus cystectomy alone in patients with locally advanced bladder cancer (T2 to T4a, N0, M0) was a result of the collaborative efforts of SWOG, the Eastern Cooperative Oncology Group (ECOG), and the Cancer and Leukemia Group B (CALGB). A total of 307 eligible patients were randomized to MVAC followed by cystectomy versus cystectomy alone. Each of the eligible patients in the neoadjuvant MVAC arm received three cycles of MVAC. The objective of the study was to compare the survival of patients who received MVAC prior to cystectomy to the survival of patients who underwent only cystectomy.

Grade 4 toxicities occurred in 55 of 150 (37%) patients receiving MVAC. Other toxicities included grade 2 to 3 stomatitis (42 patients) and an increase in creatinine levels

(7 patients); 75 (50%) of patients had either grade 3 or 4 granulocytopenia toxicities, and 31 (21%) of the patients had either grade 3 or 4 toxicities related to nausea and/or vomiting. With a median follow-up of 7.1 years, there were 85 deaths in the MVAC arm and 94 deaths in the no-MVAC arm. Median survival in the MVAC arm was 6.2 years, which was statistically

Large-scale studies are needed to resolve whether neoadjuvant chemotherapy should become the standard of care.

better than the 3.8-year median survival for the no-MVAC arm, using a one-tailed analysis. The authors conclude that neoadjuvant MVAC improved survival benefit for patients with locally advanced bladder cancer. The results of the study are summarized in Table 3.⁵⁵

The results of this phase III intergroup trial are controversial and caused a spirited discussion when they were initially presented at this year's meeting of the American Society of Clinical Oncology (ASCO) in San Francisco. Proponents of neoadjuvant therapy emphasized the

lack of mortality and the lack of increased risk of surgical complications associated with MVAC. Two prior studies were also cited (MRC/EORTC and the Nordic I)^{56,57} that suggested a survival benefit. Critics have reviewed a number of large series in which neoadjuvant chemotherapy has not shown any survival benefit. The total number of patients accumulated in these studies is over 2,000.

Another area of controversy involved the statistical analyses used. If a two-sided test were used, the difference in median survival (6.2 versus 3.8 months) would not have reached statistical significance ($P = .09$). The hazard ratio would have been calculated to be 0.78 (95% CI: 0.58-1.04), with a 95% confidence level that overlapped a hazard ratio of one.

Finally, exclusion of patients with P0 disease revealed nearly equal survival curves in the MVAC arm and the no-MVAC arm. One could draw the conclusion that patients with residual disease after transurethral resection of bladder tumor (TURBT) did not gain any survival advantage with

neoadjuvant MVAC. In addition, the P0 patients might have done just as well without MVAC.

Future large-scale studies are needed to resolve whether neoadjuvant chemotherapy should become the standard of care. While urologists should discuss the findings of the SWOG study when counseling their patients, consideration should be given to administering chemotherapy in an adjuvant setting based on surgical pathology. This would potentially spare patients the morbidities associated with chemotherapy, especially in patients who might not otherwise

need adjuvant therapy. Furthermore, waiting for the final pathology also prevents delays in cystectomy, which could otherwise lead to progression of disease.⁵⁸

[Ken-ryu Han, MD, Allan J. Pantuck, MD, Amnon Zisman, MD, Matthew H.T. Bui, MD, PhD, Arie S. Beldegrun, MD, FACS]

Improved Prognostication of Renal Cell Carcinoma Using an Integrated System

It is commonly accepted that tumor stage is the most important predictor of clinical behavior for renal cell carcinoma (RCC). The two staging systems that are the most commonly used include Robson's⁵⁹ original staging system and the tumor-node-metastasis (TNM) system, which was recently modified in 1997 by the International Union against Cancer.⁶⁰ In addition to stage, it has become apparent that other variables such as patients' performance status (PS)⁶¹ and grade⁶²

may also impact survival outcome.⁶³ In fact, the ECOG PS is often used as an inclusion criteria for admission into immunotherapy and vaccine trials.

In an effort better to predict the clinical outcome of patients with RCC, Zisman and colleagues at the University of California at Los Angeles (UCLA) recently developed a novel new staging system which was

clinical outcome. They determined UISS staging for each of the patients by 1) AJCC 1997 TNM staging I to IV; 2) Furman grades 1 to 4; and 3) ECOG PS with a "0" score given for full activity and higher numbers given as activity levels decreased. UISS stage 1 was given the most favorable combination of these three variables (ie, TNM I, Fuhrman grade 1, and ECOG

This integrated system may become an important prognostic tool for counseling patients with various stages of renal cell carcinoma.

presented at this year's AUA meeting.⁶⁴ The UCLA Integrated Staging System (UISS) combines the 1997 TNM staging system, Furman's grade,⁶⁵ and ECOG PS into five UISS categories.⁶⁶

In a review of 661 patients who underwent radical or partial nephrectomy, Zisman and colleagues confirmed that the above three variables were prognostic in terms of predicting

PS 0) and UISS stage 5 included TNM IV, Fuhrman grade 4, and an ECOG PS at or over 1. The other three UISS stages fell in between. Five-year survival rates for each of the five UISS stages from 1 to 5 were 94%, 67%, 39%, 23%, and 0%, respectively.

By combining the three variables of TNM stage, Fuhrman grade, and ECOG PS, this integrated system may

Main Points

- The amplitude of fast-twitch muscle contractions was decreased in denervated sphincters and was improved by approximately 88% in denervated sphincters injected with muscle-derived stem cells.
- Recent prospective randomized controlled studies have shown active electromagnetic therapy may be superior to placebo; finasteride to bring greater symptom relief than saw palmetto; and rofecoxib 50 mg to produce greater improvements in more patients with CP/PPS than placebo.
- Complex PSA and the computed complex PSA (defined as total PSA minus free PSA) were more specific than the free-to-total PSA ratio in detecting prostate cancer.
- MRI provides superior morphologic imaging over ultrasound and renal scintigraphy; no difference was found in the relative renal function calculated by MRI and by renal scintigraphy.
- Laparoscopic retroperitoneal radical nephroureterectomy has become the standard in treating those select patients with upper urinary tract transitional cell carcinoma who require extirpative surgery.
- An examination of data gathered worldwide supports the argument that widespread PSA testing correlates to lower prostate cancer mortality rates.
- A sequence of three abstracts presented at the AUA represents one of the best translational research efforts to further our understanding of the mechanism of action of saw palmetto extract in men with LUTS and clinical BPH on hormonal, cellular, and molecular levels.
- A randomized phase III trial of neoadjuvant methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC) and cystectomy versus cystectomy alone in patients with locally advanced bladder cancer produced controversial results.
- The UCLA Integrated Staging System (UISS) combines the 1997 TNM staging system, Furman's grade, and ECOG PS into five UISS categories.

become an important prognostic tool for counseling patients with various stages of renal cell carcinoma. The UISS is simple to use and offers the advantage of accounting for pathologic grade and the patient's performance status. The future prospects for this risk stratification system await prospective, external validation.

[Ken-ryu Han MD, Amnon Zisman, MD, Allan J. Pantuck, MD, Matthew H.T. Bui, MD, PhD, Arie S. Beldegrun, MD, FACS]

Erectile Dysfunction

The most common cause of erectile dysfunction (ED) is vascular (ie, failure of blood to be trapped in the penis). Current evidence suggests that this is probably due to a myopathy of the corporal smooth muscle, in that the smooth muscle becomes defective or is collagenized. In fact, biopsies of the smooth muscle of men with ED demonstrate a decrease in smooth muscle content and an increase in fibrosis. Well, what if one could make new corporal smooth muscle and put it into the corpora to do what it is supposed to do in that organ? This may be a reality one day, based on the pioneering work of Atala and colleagues, who presented data at the 2001 AUA meeting demonstrating their preliminary attempts to manufacture new muscle cells via nuclear transfer.⁶⁷ They reported that these engineered cells can be successfully harvested, expanded in culture, and transplanted in vivo, where the single cells form and organize into muscle structures genetically similar to the host tissue. The day of wishing for a penis that continues to be functional for as long as we live gets closer to being fact than fiction. ■

[Jacob Rajfer, MD]

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